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Patent Office

(11) (C) 1,324,383

(21) 552,085

(22) 1987/11/18

(45) 1993/11/16

(52) 260-308
C.L. CR. 167-233

(51) INTL.CL.[5] C07F-009/547; A61K-031/41

(19)(CA) **CANADIAN PATENT** (12)

(54) Process for the Manufacture of Novel Substituted Aminomethanediphosphonic Acids

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(30) (CH) Switzerland 4665/86-9 1986/11/21

(57) 14 Claims

NO DRAWING

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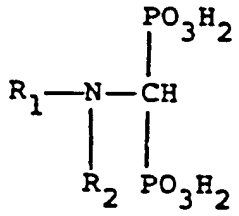
Process for the manufacture of novel substituted aminomethanediphosphonic acids

The invention relates to a process for the manufacture of novel substituted aminomethanediphosphonic acids, especially of heteroarylaminomethanediphosphonic acids of the formula



(I)

in which R_1 represents an optionally benzo- or cyclohexeno-fused 5-membered heteroaryl radical that contains, as hetero atom(s), either from 2 to 4 N-atoms or 1 or 2 N-atoms as well as 1 O-atom or S-atom and that is unsubstituted or is C-substituted by lower alkyl; by phenyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy and/or by halogen; by lower alkoxy; by hydroxy; by di-lower alkylamino; by lower

alkylthio and/or by halogen; and/or that is N-substituted by lower alkyl; or by phenyl-lower alkyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy and/or by halogen; and R_2 represents hydrogen or lower alkyl, with the proviso that R_2 is other than hydrogen when R_1 represents a pyrazol-3-yl or isoxazol-3-yl radical that is optionally substituted by alkyl and/or by halogen, and of their salts.

Optionally benzo- or cyclohexeno-fused 5-membered heteroaryl radicals containing, as hetero atom(s), either from 2 to 4 N-atoms or 1 or 2 N-atoms as well as 1 O-atom or S-atom are, for example, imidazolyl, for example imidazol-2-yl or -4-yl, thiazolyl, for example thiazol-2-yl, or also thiazol-5-yl or -4-yl, oxazolyl, for example oxazol-2-yl, or also oxazol-4-yl, triazolyl, for example 4H-1,2,4-triazol-3-yl or 2H-1,2,3-triazol-4-yl, tetrazolyl, for example tetrazol-5-yl, thiadiazolyl, for example 1,2,5-thiadiazol-3-yl, oxadiazolyl, for example 1,3,4-oxadiazol-2-yl, benzimidazolyl, for example benzimidazol-2-yl, benzoxazolyl, for example benzoxazol-2-yl, or benzothiazolyl, for example benzothiazol-2-yl. The radicals mentioned may contain one or several identical or different, especially one or two identical or different, substituents from among those mentioned at the beginning. Radicals R_1 having substitutable N-atoms are preferably N-substituted as indicated. Radicals R_1 are, for example, 1-C_1-C_4-alkylimidazol-2-yl radicals, such as 1-methylimidazol-2-yl, 1-phenyl-C_1-C_4-alkylimidazol-2-yl radicals, such as 1-benzylimidazol-2-yl, oxazol-2-yl, thiazol-2-yl, 4- and 5-C_1-C_4-alkylthiazol-2-yl radicals, such as 4- or 5-methylthiazol-2-yl, 5-phenylthiazol-2-yl, 1,2,4-thiadiazol-5-yl, 3-phenyl-1,2,4-thiadiazol-5-yl,

1,3,4-thiadiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl, benzoxazol-2-yl and benzothiazol-2-yl.

Hereinbelow, there is to be understood by lower radicals and compounds, for example, those containing up to and including 7, especially up to and including 4, C-atoms. In addition, the general terms have, for example, the following meanings:

Lower alkyl is, for example, C_1-C_4-alkyl, such as methyl, ethyl, propyl or butyl, or also iso-, sec.- or tert.-butyl, but may also be a C_5-C_7-alkyl group, such as a pentyl, hexyl or heptyl group.

Phenyl-lower alkyl is, for example, phenyl-C_1-C_4-alkyl, especially 1-phenyl-C_1-C_4-alkyl, such as benzyl.

Lower alkoxy is, for example, C_1-C_4-alkoxy, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy or tert.-butoxy.

Di-lower alkylamino is, for example, di-C_1-C_4-alkylamino, such as dimethylamino, diethylamino, N-ethyl-N-methylamino, dipropylamino, N-methyl-N-propylamino or dibutylamino.

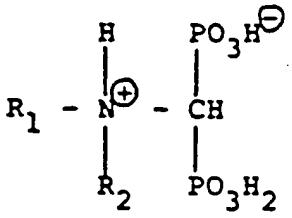
Lower alkylthio is, for example, C_1-C_4-alkylthio, such as methylthio, ethylthio, propylthio or butylthio, or also iso-, sec.- or tert.-butylthio.

Halogen is, for example, halogen having an atomic number of up to and including 35, such as fluorine, chlorine or bromine.

Salts of compounds of the formula I are especially the salts thereof with pharmaceutically acceptable bases, such as non-toxic metal salts derived from metals of groups Ia, Ib, IIa and IIb, for example alkali metal salts, especially sodium or potassium salts, alkaline earth metal salts, especially calcium or magnesium salts, copper salts, aluminium salts or zinc salts, or ammonium salts with ammonia or organic amines or quaternary ammonium bases, such as optionally

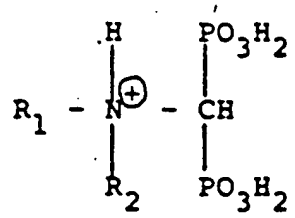
C-hydroxylated aliphatic amines, especially mono-, di- or tri-lower alkylamines, for example methyl-, ethyl-, dimethyl- or diethyl-amine, mono-, di- or tri-(hydroxy-lower alkyl)-amines, such as ethanol-, diethanol- or triethanol-amine, tris(hydroxymethyl)amino-methane or 2-hydroxy-tert.-butylamine, or N-(hydroxy-lower alkyl)-N,N-di-lower alkylamines or N-(polyhydroxy-lower alkyl)-N-lower alkylamines, such as 2-(dimethylamino)-ethanol or D-glucamine, or quaternary aliphatic ammonium hydroxides, for example tetrabutylammonium hydroxide.

It should also be mentioned in this connection that the compounds of the formula I may be in the form of internal salts, for example of the formula



(I').

The mentioned compounds can accordingly also be converted, by treatment with a strongly protonic acid, such as with a hydrohalic acid, sulphuric acid, sulphonic acid, for example methane- or p-toluene-sulphonic acid, or sulphamic acid, for example N-cyclohexylsulphamic acid, into the corresponding acid addition salts of the formula



(I"),

in which $A^{\ominus}$ represents the anion of the protonic acid.

The compounds of the formula I and their salts have valuable pharmacological properties. In particular, they exhibit a pronounced regulatory action on the calcium metabolism of warm-blooded animals. In particular, in rats, they bring about pronounced inhibition of bone resorption, which can be demonstrated both in the test procedure according to Acta Endocrinol. 78, 613-24 (1975) by reference to the PTH-induced increase in the serum calcium level after subcutaneous administration in doses of from approximately 0.01 to approximately 1.0 mg/kg, and in the TPTX (thyroparathyroidectomised) rat model by reference to the experimental hypercalcaemia, induced by vitamin D_3, after the administration of doses of approximately from 0.001 to 1.0 mg s.c.. The tumour hypercalcaemia induced by Walker-256-tumours is likewise inhibited after peroral administration of from approximately 1.0 to approximately 100 mg/kg. Further, in adjuvant arthritis in rats in the test procedure according to Newbould, Brit. J. Pharmacology 21, 127 (1963) and according to Kaibara et al., J. Exp. Med. 159, 1388-96 (1984), they exhibit a marked inhibition of the progression of chronic arthritic processes in doses of approximately from 0.01 to 1.0 mg/kg s.c.. They are therefore excellently suitable as active ingredients in medicaments for the treatment of illnesses that can be

attributed to calcium metabolism disorders, for example inflammatory processes in joints and degenerative processes in the arthrodial cartilage, of osteoporosis, periodontitis, hyperparathyroidism and of calcium deposits in blood vessels or on prosthetic implants. A favourable effect is produced both in illnesses in which an anomalous deposition of sparingly soluble calcium salts is to be observed, such as those from among the forms of arthritis, for example Morbus Bechterew, neuritis, bursitis, periodontitis and tendinitis, fibrodysplasia, osteoarthrosis and of artereosclerosis, and in those illnesses in which an anomalous degeneration of hard body tissue is well to the fore, such as hereditary hypophosphatasis, degenerative processes in the arthrodial cartilage, osteoporoses of various origins, Morbus Paget and osteodystrophia fibrosa, and also in tumour-induced osteolytic processes.

The invention relates especially to the manufacture of compounds of the formula I in which R_1 represents an imidazolyl, benzimidazolyl, 2H-1,2,3- or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, benzoxazolyl, oxadiazolyl, thiazolyl, benzothiazolyl or thiadiazolyl radical that is C-unsubstituted or C-mono- or C-di-substituted by lower alkyl; by lower alkoxy; by phenyl that is unsubstituted or is mono- or di-substituted by lower alkyl, lower alkoxy and/or by halogen; by hydroxy; by di-lower alkylamino; by lower alkylthio and/or by halogen; and that is unsubstituted at a substitutable N-atom which may optionally be present or preferably N-mono- or N-di-substituted by lower alkyl or by phenyl-lower alkyl that is unsubstituted or is mono- or di-substituted by lower alkyl, lower alkoxy and/or by halogen; and R_2 represents hydrogen or lower alkyl, and of their salts, especially their internal salts and pharmaceutically acceptable salts with bases.

The invention relates especially, for example, to the manufacture of compounds of the formula I in which R_1 represents an imidazolyl, benzimidazolyl, 2H-1,2,3- or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, benzoxazolyl, oxadiazolyl, thiazolyl, benzothiazolyl or thiadiazolyl radical that is unsubstituted or is mono- or di-substituted by lower alkyl; by lower alkoxy; by phenyl that is unsubstituted or is mono- or di-substituted by lower alkyl, lower alkoxy and/or by halogen; by hydroxy; by di-lower alkylamino; by lower alkylthio and/or by halogen; and R_2 represents hydrogen or lower alkyl, and of their salts, especially their internal salts and pharmaceutically acceptable salts with bases.

The invention relates especially to the manufacture of compounds of the formula I in which R_1 represents a thiazolyl, such as thiazol-2-yl, radical, a benzothiazol-2-yl radical, a thiadiazolyl, such as 1,2,4-thiadiazol-5-yl or 1,3,4-thiadiazol-2-yl, radical, an oxazolyl, such as oxazol-2-yl, radical or a benzoxazol-2-yl radical each of which is unsubstituted or is C-substituted by C_1-C_4-alkyl, such as methyl, or by a phenyl radical that is unsubstituted or is mono- or di-substituted by C_1-C_4-alkyl, such as methyl, C_1-C_4-alkoxy, such as methoxy, and/or by halogen, such as chlorine; or represents an imidazolyl, such as imidazol-2-yl or imidazol-4-yl, radical or a benzimidazol-2-yl radical each of which is unsubstituted or is C-substituted by C_1-C_4-alkyl, such as methyl, or by a phenyl radical that is unsubstituted or is mono- or di-substituted by C_1-C_4-alkyl, such as methyl, C_1-C_4-alkoxy, such as methoxy, and/or by halogen, such as chlorine, and/or each of which is N-substituted by C_1-C_4-alkyl, such as methyl, or by a phenyl-C_1-C_4-alkyl radical, such as a benzyl radical, that is unsubstituted or is mono- or di-substituted by C_1-C_4-alkyl, such as methyl, C_1-C_4-alkoxy, such as methoxy, and/or by halogen, such as chlorine; and R_2

represents hydrogen, and of their salts, especially their internal salts and pharmaceutically acceptable salts with bases.

The invention relates more especially to the manufacture of compounds of the formula I in which R_1 represents a thiazolyl, such as thiazol-2-yl or thiazol-4-yl, radical that is unsubstituted or is substituted by C_1-C_4-alkyl, such as methyl, by C_1-C_4-alkoxy, such as methoxy, by phenyl, by hydroxy, by di-C_1-C_4-alkylamino, such as dimethylamino or diethylamino, by C_1-C_4-alkylthio, such as methylthio, or by halogen having an atomic number of up to and including 35, such as chlorine, and R_2 represents hydrogen, and of their salts, especially their internal salts and pharmaceutically acceptable salts with bases.

The invention relates even more especially to the manufacture of compounds of the formula I in which R_1 represents a thiazolyl, such as thiazol-2-yl, radical, a 1-C_1-C_4-alkyl-, such as 1-methyl-imidazol-2-yl or -4-yl, radical, or a phenyl-C_1-C_4-alkyl-, such as benzyl-imidazol-2-yl or -4-yl, radical each of which is unsubstituted or is C-substituted by C_1-C_4-alkyl, such as methyl, by C_1-C_4-alkoxy, such as methoxy, by phenyl, by hydroxy, by di-C_1-C_4-alkylamino, such as dimethylamino or diethylamino, by C_1-C_4-alkylthio, such as methylthio, or by halogen having an atomic number of up to and including 35, such as chlorine, and R_2 represents hydrogen, and of their salts, especially their internal salts and pharmaceutically acceptable salts with bases.

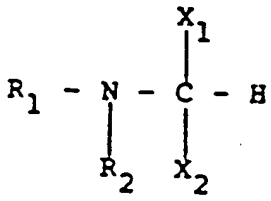
The invention relates most especially to the manufacture of compounds of the formula I in which R_1 represents a thiazol-2-yl radical that is unsubstituted or is mono- or disubstituted, especially in the 4- and/or 5-position, by C_1-C_4-alkyl, such as methyl, or by phenyl, or represents an imidazol-2-yl or benzimidazol-2-yl radical that is unsubstituted or is mono-substituted in

the 1-position by C_1-C_4-alkyl, such as methyl, or by phenyl-C_1-C_4-alkyl, such as benzyl, respectively, or represents an unsubstituted benzoxazol-2-yl or benzothiazol-2-yl radical, and R_2 represents hydrogen, and of their salts, especially their internal salts and pharmaceutically acceptable salts with bases.

The invention relates specifically to the manufacture of the compounds of the formula I mentioned in the Examples and of their salts, especially their internal salts and pharmaceutically acceptable salts with bases.

The invention process for the manufacture of compounds of the formula I and to their salts is based on methods that are known per se and is characterised in that

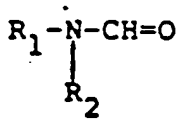
a) in a compound of the formula



(II)

which is optionally intermediately protected at a substitutable N-atom of the radical R_1 and in which X_1 represents a functionally modified phosphono group X and X_2 represents phosphono or similarly represents a functionally modified phosphono group X, the group(s) X is(are) converted into free phosphono, or

b) a compound of the formula

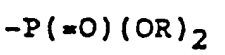


(III),

which is optionally intermediately protected at a substitutable N-atom of the radical R_1, is reacted first with phosphorus trioxide and then with water,

and, if desired, in each case, a resulting compound is converted into a different compound of the formula I and/or a resulting free compound is converted into a salt or a resulting salt is converted into the free compound or into a different salt.

Functionally modified phosphono groups X that are to be converted into free phosphono according to process variant a) are, for example, in the form of an ester, especially in the form of a diester of the formula



(IIa)

in which OR represents, for example, lower alkoxy, or a phenoxy group that is optionally substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl and/or by hydroxy.

The conversion of a functionally modified phosphono group into a free phosphono group is effected in customary manner by hydrolysis, for example in the presence of a mineral acid, such as hydrochloric or hydrobromic acid or sulphuric acid, or by reaction with a tri-lower alkyl-halosilane, for example with trimethylchlorosilane or, especially, trimethyliodosilane or trimethylbromosilane, preferably while cooling, for example in a temperature range of from

approximately 0° to approximately 25°C.

The starting materials of the formula II can be manufactured, for example, by condensing a compound of the formula

$$R_1\text{-}N(R_2)\text{-}H \qquad (IIb;\ R_2=H)$$

with at least the equimolar amount of an orthoformic acid triester of the formula

$$H\text{-}C(OR)_3 \qquad (IIc)$$

in which OR represents, for example, lower alkoxy, or a phenoxy group that is optionally substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl and/or by hydroxy, there probably being formed initially a corresponding compound of the formula

$R_1\text{-}NH\text{-}CH(OR)_2$ (IId1) or $R_1\text{-}N{=}CH\text{-}OR$ (IId2),

and by further reacting the condensation product with at least double the molar amount of a phosphorous acid diester, for example of the formula

$$H\text{-}\overset{\overset{O}{\|}}{P}(OR)_2 \qquad (IIe),$$

and, if desired, lower alkylating the resulting compound (II, R_2=H) to form the corresponding compound (II; R_2= lower alkyl).

In intermediates II in which the radical R_1 is N-substituted by lower alkyl or by phenyl-lower alkyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy and/or by halogen, the N-substituent can be removed, lower alkyl being removed, for example, by treatment with a haloformic acid ester, such as a

bromoformic or chloroformic acid lower alkyl ester, and subsequent hydrolysis of the resulting carbamate, and α-phenyl-lower alkyl radicals being removed, for example, by hydrogenolysis, for example by treatment with hydrogen in the presence of a hydrogenation catalyst, for example palladium-on-carbon and/or platinum oxide, or by reduction with a metal, for example by treatment with an alkali metal in ammonia.

It is also possible, however, to react the starting material IIb in a manner known per se with the phosphorous acid diester IIe in the presence of an orthoformic acid triester IIc without isolating the intermediate stage. Thus, according to an especially preferred embodiment, the corresponding compound IIb is reacted at boiling heat in the presence of at least the equimolar amount of an orthoformic acid triester IIc with at least double the molar amount of the phosphorous acid diester IIe without isolating the intermediate stage, for example of the formula IId1 or IId2, and the primary product II is hydrolysed by treatment with aqueous hydrochloric acid at boiling heat.

The reaction of compounds III with phosphorus trioxide according to process variant b) is preferably effected with the latter being formed in situ, for example by reacting phosphorus trichloride and phosphorous acid at elevated temperature, for example at approximately from 50 to 65°C, adding the reactant III, heating further and working up the primary product, a 1:1 adduct of the aldehyde of the formula

$$R_1-\underset{\displaystyle R_2}{\overset{|}{N}}-CH=O \qquad (III)$$

with phosphorus trioxide of hitherto-unknown structure, by hydrolysis, preferably by treatment with water.

In a modification of this preferred embodiment of

process variant b), orthophosphoric acid is reacted, at approximately from 50°C to 70°C, with an approximately 1.1- to approximately 2-fold, preferably approximately 1.5-fold, excess of phosphorus trichloride, the reactant III is added, the whole is heated for a prolonged period at approximately from 50°C to 70°C, diluted with 80% phosphoric acid and worked up by hydrolysis.

Starting materials III can be manufactured in customary manner, for example by reacting an amine of the formula

$$R_1\text{-}N(R_2)\text{-}H \qquad \text{(IIb; R=H)}$$

with formic acid or a functional carboxy derivative thereof, for example with a formic acid ester of the formula

$$H\text{-}COOR \qquad \text{(IIe)}$$

in which OR represents, for example, a phenoxy group that is optionally substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl and/or by hydroxy, or with formamide.

For the intermediate protection of a substitutable N-atom of the radical R_1 the customary N-protecting groups and methods of introducing and removing them are suitable, for example 2,2,2-trihaloethoxycarbonyl radicals, such as 2,2,2-triiodo-, 2,2,2-tribromo- or 2,2,2-trichloro-ethoxycarbonyl radicals, which can be removed, for example, by treatment with zinc in acetic acid, α-phenyl-lower alkoxycarbonyl radicals, such as benzyloxycarbonyl, which can be removed, for example, by catalytic hydrogenation, and lower alkanesulphonyl groups, such as methanesulphonyl, which can be removed, for example, by treatment with bis(2-methoxyethoxy)-sodium aluminium hydride, and also, however, α-phenyl-

alkyl or alkyl groups, the removal of which is dealt with hereinafter.

Compounds of the formula I obtained in accordance with the process of the invention or by another process that is known per se can be converted into other compounds of the formula I in a manner known per se.

For example, lower alkyl R_2 can be introduced into compounds of the formula I in which R_2 represents hydrogen by reaction with a reactive ester, such as a hydrohalic acid ester or an organic sulphonic acid ester, of a lower alkanol. It is also possible, however, to introduce an aliphatic radical, for example methyl, by reaction with an aliphatic aldehyde, for example with formaldehyde and formic acid.

It is also possible in compounds of the formula I in which the radical R_1 is N-substituted by lower alkyl or by phenyl-lower alkyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy and/or by halogen, to remove the N-substituent, lower alkyl being removed, for example, by treatment with a haloformic acid ester, such as a bromoformic or chloroformic acid lower alkyl ester, and subsequent hydrolysis of the resulting carbamate, and α-phenyl-lower alkyl radicals being removed, for example, by hydrogenolysis, for example by treatment with hydrogen in the presence of a hydrogenation catalyst, for example palladium-on-carbon and/or platinum oxide, or by reduction with a metal, for example by treatment with an alkali metal in ammonia.

Resulting free compounds of the formula I, including their internal salts of the formula I', can be converted into salts with bases by partial or complete neutralisation with one of the bases mentioned at the beginning. Acid addition salts of the formula I" also can be converted in an analogous manner into the corresponding free compounds of the formula I or internal salts of the formula I'.

Conversely, resulting free compounds of the formula I can be converted into acid addition salts of the formula I" by treatment with one of the protonic acids mentioned at the beginning.

Resulting salts can be converted into the free compounds in a manner known per se, for example by treatment with an acid reagent, such as a mineral acid, or, as the case may be, with a base, for example alkali liquor.

The compounds, including their salts, may also be obtained in the form of their hydrates or may include the solvent used for crystallisation.

Owing to the close relationship between the novel compounds in free form and in the form of their salts, hereinbefore and hereinafter there is to be understood by the free compounds or their salts, where appropriate and expedient, optionally also the corresponding salts or free compounds, respectively.

The invention relates also to those embodiments of the process according to which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining steps are carried out or a starting material in the form of a salt and/or racemate or antipode is used or especially is formed under the reaction conditions.

The starting materials that are used in the process of the present invention are preferably those which result in the compounds described at the beginning as being especially valuable. The invention relates also to novel starting materials and processes for the manufacture thereof.

The invention relates also to pharmaceutical compositions containing, as the active ingredient, a known compound of the formula I, wherein R_2 represents a pyrazol-3-yl or isoxazol-3-yl radical that is unsubstituted or mono- or disubstituted by lower alkyl and/or halogen and R_2 denotes hydrogen, specifically 1-(isoxazol-3-ylamino)methane-1,1-diphosphonic acid, 1-(4-methylisoxazol-3-ylamino)methane-1,1-diphosphonic acid, 1-(5-methylisoxazol-3-ylamino)methane-1,1-diphosphonic acid, 1-(pyrazol-3-ylamino)methane-1,1-diphosphonic acid, 1-(4-methylpyrazol-3-ylamino)methane-1,1-diphosphonic acid or 1-(5-methylpyrazol-3-ylamino)methane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof, to the use of the active ingredient as a medicament and to a method of treatment of illnesses associated with calcium metabolism disorders.

The pharmaceutical preparations, which contain compounds of the formula I or pharmaceutically acceptable salts thereof, are for enteral, such as oral or rectal, and parenteral administration and contain the pharmacological active ingredient on its own or together with a pharmaceutically acceptable carrier. The dosage of the active ingredient depends upon the species of warm-blooded animal, its age and individual condition and also on the mode of administration. In a normal case, the estimated approximate daily dose for a warm-blooded animal of approximately 75 kg body weight is approximately from 20 to 1000 mg, preferably approximately from 30 to 300 mg, in the case of oral administration and approximately from 1 to 25 mg, preferably approximately from 1 to 10 mg, in the case of intravenous administration, the dose advantageously being divided into several equal partial doses.

The pharmaceutical preparations contain, for example, from approximately 10% to approximately 80%, preferably from approximately 20% to approximately 60%, active ingredient. Pharmaceutical preparations according to the invention for enteral and parenteral administration are, for example, those in dosage unit form, such as dragées, tablets, capsules or suppositories, and also ampoules. These are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical preparations for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture and, if desired or necessary, processing the mixture or granulate, after the addition of suitable adjuncts, into tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatine, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Adjuncts are especially flow-regulating and lubricating agents, for example silica, talc, stearic acid or salts thereof,

such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable coatings which may be resistant to gastric juices, there being used, inter alia, concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in suitable organic solvents or solvent mixtures, or, for the preparation of coatings that are resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Other orally administrable pharmaceutical preparations are dry-filled capsules consisting of gelatine, and also soft sealed capsules consisting of gelatine and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, if desired, stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also to add stabilisers.

Suitable rectally administrable pharmaceutical

preparations are, for example, suppositories that consist of a combination of the active ingredient with a suppository base material. Suitable suppository base materials are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. It is also possible to use gelatine rectal capsules that contain a combination of the active ingredient with a base material; suitable base materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

For parenteral administration there are suitable, especially, aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, or suspensions of the active ingredient, such as corresponding oily injection suspensions in which suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, are used, or aqueous injection suspensions that contain vicosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran and, if desired, also stabilisers.

The present invention relates also to the use of the compounds of the formula I and their salts, preferably for the treatment of illnesses that can be attributed to calcium metabolism disorders, for example of the rheumatic type, and especially of osteoporoses.

Dosages under 0.01 mg/kg body weight have only a negligible effect on pathological calcification or the degeneration of hard tissue. At dosages above 100 mg/kg body weight, toxic side-effects may occur in long-term use. The compounds of the formula I and their salts can be administered both orally and, in the form of a hypertonic solution, subcutaneously, intramuscularly or intravenously. The preferred daily doses are in the range of approximately from 0.1 to 5 mg/kg in the

case of oral administration, in the range of approximately from 0.1 to 1 mg/kg in the case of subcutaneous and intramuscular administration and in the range of approximately from 0.01 to 2 mg/kg in the case of intravenous administration.

The dosage of the compounds used is, however, variable and depends on the particular conditions, such as nature and severity of the illness, duration of treatment and on the particular compound. Single doses contain, for example, from 0.01 to 10 mg, dosage unit forms for parenteral, such as intravenous, administration contain, for example, from 0.01 to 0.1 mg, preferably 0.02 to 0.08 mg, and oral dosage unit forms contain, for example, from 0.2 to 2.5 mg, preferably from 0.3 to 1.5 mg, per kg of body weight. The preferred individual dosage for oral administration is from 10 to 100 mg and for intravenous administration from 0.5 to 5 mg and can be administered in up to 4 single doses per day. The higher dosages in the case of oral administration are necessary owing to the limited resorption. In the case of long-term treatments, the initially higher dosage can normally be converted to low dosages while still maintaining the desired effect.

The following Examples illustrate the invention described above; they are not intended, however, to limit the scope thereof in any way. Temperatures are given in degrees Celsius.

Example 1: 6.57 g (17 mmol) of 1-(thiazol-2-ylamino)-methane-1,1-diphosphonic acid tetraethyl ester are dissolved in 70 ml of N hydrochloric acid and heated under reflux for 6 hours. In the course of the reaction, the product separates out in the form of a fine white precipitate. After cooling to room temperature, filtration is carried out and the product is washed with aqueous methanol. 4.33 g (93% of the theoretical yield) of 1-(thiazol-2-ylamino)methane-1,1-diphosphonic acid of m.p. 275° (decomposition) are obtained.

The starting material can be prepared, for example, in the following manner:

A mixture consisting of 10.0 g (0.1 mol) of 2-aminothiazole, 20.0 ml (0.12 mol) of orthoformic acid triethyl ester and 26.6 ml (0.2 mol) of diethyl phosphite is heated under reflux for 1 hour. The ethanol liberated is distilled off, the internal temperature gradually increasing to approximately 150°. The residue is taken up in chloroform and filtered over silica gel. The crude product is purified by column chromatography (silica gel/ethyl acetate). 4.37 g (11% of the theoretical yield) of 1-(thiazol-2-ylamino)-methane-1,1-diphosphonic acid tetraethyl ester of m.p. 103-104° are obtained.

Example 2: In a manner analogous to that described in Example 1 it is also possible to prepare 1-(oxazol-2-ylamino)methane-1,1-diphosphonic acid of m.p. 245° (decomposition) and 1-(benzoxazol-2-ylamino)methane-1,1-diphosphonic acid of m.p. 270° (decomposition).

Example 3: 4.36 g (10 mmol) of 1-(benzothiazol-2-ylamino)methane-1,1-diphosphonic acid tetraethyl ester are heated in 40 ml of N hydrochloric acid at 110-120° for 6 hours. In the course of the reaction, the product

separates out in the form of a white precipitate. After cooling to room temperature, filtration is carried out and the product is washed with aqueous methanol. 3.09 g (95% of the theoretical yield) of 1-(benzothiazol-2-ylamino)methane-1,1-diphosphonic acid of m.p. 290° (decomposition) are obtained.

The starting material can be prepared, for example, in the following manner:

A mixture consisting of 3.0 g (20 mmol) of 2-aminobenzothiazole, 4.0 ml (24 mmol) of orthoformic acid triethyl ester and 5.3 ml (40 mmol) of diethyl phosphite is heated at 120-125° for 5 hours. The yellow precipitate which separates out at the beginning of the reaction gradually goes into solution again. The ethanol liberated is distilled off during the reaction. The crude product, which solidifies on being left to stand, is purified by column chromatography (silica gel/ethyl acetate/methanol). 5.62 g (64% of the theoretical yield) of 1-(benzothiazol-2-ylamino)methane-1,1-diphosphonic acid tetraethyl ester of m.p. 165-167° are obtained.

Example 4: 1.30 g (3.2 mmol) of 1-(4-methylthiazol-2-ylamino)methane-1,1-diphosphonic acid tetraethyl ester are heated in 20 ml of 1N hydrochloric acid at 100° for 20 hours. After cooling, 20 ml of methanol are added. During subsequent stirring, the product separates out in the form of fine white crystals. The filtrate is subsequently washed with methanol and petroleum ether. Yield: 615 mg (67% of the theoretical yield) of 1-(4-methylthiazol-2-ylamino)methane-1,1-diphosphonic acid of m.p. 294° (decomposition).

The starting material can be prepared, for example, in the following manner:

A mixture consisting of 2.33 g (20 mmol) of 2-amino-4-methylthiazole, 4.0 ml (24 mmol) of

orthoformic acid triethyl ester and 5.3 ml (40 mmol) of diethyl phosphite is heated at 120-125° for 4 hours. The ethanol liberated is distilled off. The residue is purified by column chromatography (silica gel/ethyl acetate/methanol). 1.32 g (17% of the theoretical yield) of 1-(4-methylthiazol-2-ylamino)methane-1,1-diphosphonic acid tetraethyl ester are obtained in the form of a viscous oil.

Example 5: 1.97 g (4.9 mmol) of 1-(5-methylthiazol-2-ylamino)methane-1,1-diphosphonic acid tetraethyl ester are heated under reflux in 20 ml of N hydrochloric acid for 6 hours. Upon cooling and leaving the reaction mixture to stand at room temperature, the product crystallises. It is filtered and washed with acetone and petroleum ether. Yield: 0.64 g (45% of the theoretical yield) of 1-(5-methylthiazol-2-ylamino)-methane-1,1-diphosphonic acid of m.p. 208° (decomposition).

The starting material can be prepared, for example, in the following manner:

A mixture consisting of 1.14 g (10 mmol) of 2-amino-5-methylthiazole, 2.0 ml (12 mmol) of orthoformic acid triethyl ester and 2.65 ml (20 mmol) of diethyl phosphite is heated at 120-125° for 4½ hours. The ethanol liberated is distilled off. The residue is purified by column chromatography (silica gel/ethyl acetate/methanol). 1.97 g (49% of the theoretical yield) of 1-(5-methylthiazol-2-ylamino)methane-1,1-diphosphonic acid tetraethyl ester are obtained in the form of a viscous oil.

Example 6: 4.02 g (8.7 mmol) of 1-(5-phenylthiazol-2-ylamino)methane-1,1-diphosphonic acid are heated under reflux in 30 ml of N hydrochloric acid for 18 hours. After cooling to room temperature, a small quantity of

methanol is added and the whole is filtered. The filtrate is heated under reflux in methanol for 1 hour, filtered while hot and washed twice with hot methanol. Yield: 2.90 g (95% of the theoretical yield) of 1-(5-phenylthiazol-2-ylamino)methane-1,1-diphosphonic acid of m.p. 290° (decomposition).

The starting material can be prepared, for example, in the following manner:

A mixture consisting of 2.93 g (16.6 mmol) of 2-amino-5-phenylthiazole, 3.3 ml (19.9 mmol) of orthoformic acid triethyl ester and 4.4 ml (33.5 mmol) of diethyl phosphite is heated first for 2 hours at 120° and then for 2 hours at 130°. The ethanol liberated is distilled off in the course of the reaction. The product, which solidifies upon cooling, is purified by chromatography (silica gel/ethyl acetate/methanol). 4.12 g (54% of the theoretical yield) of 1-(5-phenylthiazol-2-ylamino)methane-1,1-diphosphonic acid tetraethyl ester of m.p. 151-153° are obtained.

Example 7: 2.5 g (5.96 mmol) of 1-(1-benzimidazol-2-ylamino)methane-1,1-diphosphonic acid tetraethyl ester are dissolved in 25 ml of 1N hydrochloric acid and heated at 100-110° for 26 hours. In the course of the reaction, the product separates out in the form of a fine white precipitate. It is filtered while hot and washed with water and then with methanol. 0.23 g (13% of the theoretical yield) of 1-(1-benzimidazol-2-ylamino)methane-1,1-diphosphonic acid of m.p. 265° (decomposition) is obtained.

The starting material can be prepared, for example, in the following manner:

6.66 g (50 mmol) of 2-aminobenzimidazole, 10.0 ml (60 mmol) of orthoformic acid triethyl ester and 13.3 ml (101 mmol) of diethyl phosphite are mixed together and then stirred for 2 hours at 125-130° until no more

ethanol is distilled off. The residue is purified by column chromatography (silica gel/ethyl acetate/-methanol, 9:1). 2.89 g (14% of the theoretical yield) of 1-(1-benzimidazol-2-ylamino)methane-1,1-diphosphonic acid tetraethyl ester of m.p. 169-170° are obtained.

Example 8: 7 g of phosphorus trichloride are mixed with 4.0 g of phosphorous acid and the mixture is heated, while stirring, at 60° for 1 hour. 6.12 g of N-(thiazol-2-yl)formamide are added thereto and the mixture is heated for a further 6 hours at approximately 60°. The mixture is then stirred with 30 ml of water, filtered with suction, subsequently washed with aqueous methanol and dried under reduced pressure. 2.0 g of 1-(thiazol-2-ylamino)methane-1,1-diphosphonic acid of m.p. 275° (decomposition) are obtained.

Example 9: 2.0 g (20.4 mmol) of crystalline orthophosphoric acid are stirred with 3.5 g (25.5 mmol) of phosphorus trichloride for 1 hour at 55-60°. 4.08 g (20.0 mmol) of N-(4-phenylthiazol-2-yl)formamide are then added thereto. The reaction mixture is left to stand for approximately 24 hours at 60°. For dilution, 10 ml of 80% phosphoric acid are added thereto and the whole is left to stand overnight at room temperature. It is then heated again to 60-70° and a further 1.37 g (10 mmol) of phosphorus trichloride are added thereto, the whole is further stirred for 2 hours at 60-70°, 30 ml of water and 20 ml of acetone are added and the whole is stirred for 2 hours at 60° to complete the reaction. The reaction mixture is allowed to cool to room temperature, and the fine, pale yellow precipitate is filtered off and washed with water/acetone 3:2. The residue is purified by being boiled once with water/-acetone 1:1 and twice with methanol. 180 mg (2.6% of the theoretical yield) of 1-(4-phenylthiazol-2-yl-

amino)methane-1,1-diphosphonic acid of m.p. 298° (decomposition) are obtained.

The starting material can be prepared, for example, in the following manner:

13.22 g (75 mmol) of 2-amino-4-phenylthiazole are heated at 110° for 5 hours with 40 ml of formic acid. The reaction mixture is cooled to room temperature and poured onto ice. The white precipitate which separates out is filtered and washed with ice-water. The product is purified by means of petroleum ether. 7.01 g (45.8% of the theoretical yield) of 4-(phenylthiazol-2-yl-amino)formamide of m.p. 161-164° are obtained.

Example 10: In a manner known per se, for example as described in Examples 1 to 7, it is also possible to prepare the following:
1-(imidazol-2-ylamino)methane-1,1-diphosphonic acid,
1-(imidazol-4-ylamino)methane-1,1-diphosphonic acid,
1-(1-methylimidazol-2-ylamino)methane-1,1-diphosphonic acid,
1-(tetrazol-5-ylamino)methane-1,1-diphosphonic acid,
1-(oxazol-2-ylamino)methane-1,1-diphosphonic acid,
1-(1,3,4-thiadiazol-2-ylamino)methane-1,1-diphosphonic acid,
1-(5-methyl-1,3,4-thiadiazol-2-ylamino)methane-1,1-diphosphonic acid, m.p. 260° (decomposition),
1-(3-phenyl-1,2,4-thiadiazol-5-ylamino)methane-1,1-diphosphonic acid, m.p. 198°.

Example 11: Tablets, each containing 50 mg of active ingredient, for example 1-(thiazol-2-ylamino)methane-1,1-diphosphonic acid or a salt, for example the sodium salt, thereof, can be prepared in the following manner:

Constituents (for 1000 tablets)	
active ingredient	50.0 g
lactose	50.7 g
wheat starch	7.5 g
polyethylene glycol 6000	5.0 g
talc	5.0 g
magnesium stearate	1.8 g
demineralised water	q.s.

Preparation: All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active ingredient, the lactose, the talc, the magnesium stearate and half of the starch are mixed. The other half of the starch is suspended in 40 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 ml of water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

Example 12: Tablets, each containing 100 mg of active ingredient, for example 1-(thiazol-2-ylamino)methane-1,1-diphosphonic acid or a salt, for example the sodium salt, thereof, can be prepared in the following manner:

Constituents (for 1000 tablets)	
active ingredient	100.0 g
lactose	100.0 g
wheat starch	47.0 g
magnesium stearate	3.0 g

Preparation: All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active ingredient, the lactose, the magnesium

stearate and half of the starch are mixed. The other half of the starch is suspended in 40 ml of water and this suspension is added to 100 ml of boiling water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

Example 13: In a manner analogous to that described in Examples 11 and 12, it is also possible to prepare tablets each containing 100 mg or 50 mg of another of the compounds of the formula I mentioned in Examples 1 to 10, which compounds may also be in the form of salts with bases, for example in the form of the disodium salt.

Example 14: Tablets for chewing, each containing 75 mg of active ingredient, for example 1-(thiazol-2-ylamino)methane-1,1-diphosphonic acid or a salt, for example the sodium salt, thereof, can be prepared, for example, in the following manner:

Composition: (for 1000 tablets)

active ingredient	75.0 g
mannitol	230.0 g
lactose	150.0 g
talc	21.0 g
glycine	12.5 g
stearic acid	10.0 g
saccharin	1.5 g
5% gelatine solution	q.s.

Preparation: All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the

addition of gelatine solution, forced through a sieve of 2 mm mesh width, dried at 50° and again forced through a sieve of 1.7 mm mesh width. The active ingredient, the glycine and the saccharin are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is mixed thoroughly and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking groove on the upper side.

In an analogous manner, it is also possible to prepare tablets each containing 75 mg of another of the compounds of the formula I mentioned in Examples 1 to 9, which compounds may also be in the form of salts with bases, for example in the form of the disodium salt.

Example 15: Tablets, each containing 10 mg of active ingredient, for example 1-(thiazol-2-ylamino)methane-1,1-diphosphonic acid or a salt, for example the sodium salt, thereof, can be prepared in the following manner:

Composition (for 1000 tablets)

active ingredient	10.0 g
lactose	328.5 g
corn starch	17.5 g
polyethylene glycol 6000	5.0 g
talc	25.0 g
magnesium stearate	4.0 g
demineralised water	q.s.

Preparation: The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active ingredient, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 ml of water. The resulting

paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35°, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

In an analogous manner, it is also possible to prepare tablets each containing 10 mg of another compound of the formula I according to Examples 1 to 9, which compound may also be in the form of a salt with a base, for example in the form of the disodium salt.

Example 16: Gelatine dry-filled capsules, each containing 100 mg of active ingredient, for example 1-(thiazol-2-ylamino)methane-1,1-diphosphonic acid or a salt, for example the sodium salt, thereof, can be prepared in the following manner:

Composition (for 1000 capsules)

active ingredient	350.0 g
microcrystalline cellulose	30.0 g
sodium lauryl sulphate	2.0 g
magnesium stearate	8.0 g

The sodium lauryl sulphate is sieved into the active ingredient (lyophilised) through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm mesh width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 390 mg each into size 0 (elongated) gelatine dry-fill capsules.

In an analogous manner, it is also possible to prepare capsules each containing 100 mg of another compound of the formula I according to Examples 1 to 9, which compound may also be in the form of a salt with a base, for example in the form of the disodium salt.

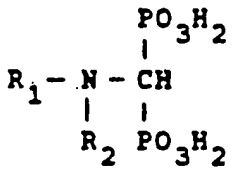
Example 17: A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

active ingredient, for example 1-(thiazol-2-ylamino)-methane-1,1-diphosphonic acid or a salt, for example the sodium salt, thereof	5.0 g
sodium chloride	22.5 g
phosphate buffer pH 7.4	300.0 g
demineralised water	to 2500.0 ml

The active ingredient is dissolved in 1000 ml of water and filtered through a microfilter. The buffer solution is added and the whole is made up to 2500 ml with water. To prepare dosage unit forms, portions of 1.0 or 2.5 ml each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 mg of active ingredient).

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

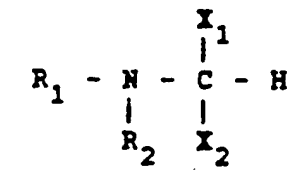
1. A process for the manufacture of a heteroarylamino-methanediphosphonic acid of the formula



(I)

in which R_1 represents an optionally benzo- or cyclohexeno-fused 5-membered heteroaryl radical that contains, as hetero atom(s), either from 2 to 4 N-atoms or 1 or 2 N-atoms as well as 1 O-atom or S-atom and that is unsubstituted or is C-substituted by lower alkyl; by phenyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy or by halogen; by lower alkoxy; by hydroxy; by di-lower alkylamino; by lower alkylthio or by halogen; or that is N-substituted by lower alkyl; or by phenyl-lower alkyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy or by halogen; and R_2 represents hydrogen or lower alkyl, with the proviso that R_2 is other than hydrogen when R_1 represents a pyrazol-3-yl or isoxazol-3-yl radical that is optionally substituted by alkyl or by halogen, and salts or a pharmaceutically acceptable salt thereof which process comprises

a) in a compound of the formula

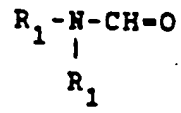


(II)

which is optionally intermediately protected at a substitutable

N-atom of the radical R_1 and in which X_1 represents a functionally modified phosphono group X and X_2 represents phosphono or similarly represents a functionally modified phosphono group X, the group(s) X is(are) converted into free phosphono, or

b) a compound of the formula



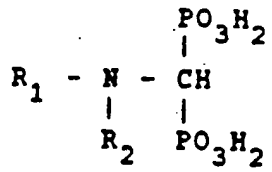
(III),

which is optionally intermediately protected at a substitutable N-atom of the radical R_1, is reacted first with phosphorus trioxide and then with water, and, if required, in each case, a resulting compound is converted into a different compound of the formula I or a resulting free compound is converted into a salt or a resulting salt is converted into the free compound or into a different salt.

2. A process according to claim 1, characterised in that a compound of the formula II, wherein X_1 and X_2 denote groups of the formula $-P(=O)(OR)_2$ (IIa) in which R represents lower alkoxy, is hydrolysed in the presence of a mineral acid.

3. A process according to claim 1, characterised in that a compound of the formula III is reacted with phosphorous trioxide formed <u>in situ</u> by reaction of a phosphorous trihalide and phosphorous or phosphoric acid, and subsequently treated with water.

4. A heteroarylaminomethanediphosphonic acid of the formula



(I)

in which R_1 represents an optionally benzo- or cyclohexeno-fused 5-membered heteroaryl radical that contains, as hetero atom(s), either from 2 to 4 N-atoms or 1 or 2 N-atoms as well as 1 O-atom or S-atom and that is unsubstituted or is C-substituted by lower alkyl; by phenyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy or by halogen; by lower alkoxy; by hydroxy; by di-lower alkylamino; by lower alkylthio or by halogen; or that is N-substituted by lower alkyl; or by phenyl-lower alkyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy or by halogen; and R_2 represents hydrogen or lower alkyl, with the proviso that R_2 is other than hydrogen when R_1 represents a pyrazol-3-yl or isoxazol-3-yl radical that is optionally substituted by alkyl or by halogen or a pharmaceutically acceptable salt thereof.

5. A compound of the formula I according to claim 4, in which R_1 represents an imidazolyl, benzimidazolyl, 2H-1,2,3- or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, benzoxazolyl, oxadiazolyl, thiazolyl, benzothiazolyl or thiadiazolyl radical that is C-unsubstituted or C-mono or C-di-substituted by lower alkyl; by lower alkoxy; by phenyl that is unsubstituted or is mono- or di-substituted by lower alkyl, lower alkoxy or by halogen; by hydroxy; by di-lower alkylamino; by lower alkylthio or

C/

by halogen; and that is unsubstituted at a substitutable N-atom which may optionally be present or preferably N-mono-substituted by lower alkyl or by phenyl-lower alkyl that is unsubstituted or is mono or di-substituted by lower alkyl, lower alkoxy or by halogen; and R_2 represents hydrogen or lower alkyl, or a pharmaceutically acceptable salt thereof.

6. A compound of the formula I according to claim 4, in which R_1 represents a thiazolyl radical, benzothiazol-2-yl radical, thiadiazolyl radical, oxazolyl radical or benzoxazol-2-yl radical each of which is unsubstituted or is C-substituted by C_1-C_4-alkyl or by a phenyl radical that is unsubstituted or is mono- or di-substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy or by halogen; or represents an imidazol-2-yl radical or benzimidazol-2-yl radical each of which is unsubstituted or is C-substituted by C_1-C_4-alkyl or by a phenyl radical that is unsubstituted or is mono- or di-substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy or by halogen, or each of which is N-substituted by C_1-C_4-alkyl or by a phenyl-C_1-C_4-alkyl radical that is unsubstituted or is mono- or di-substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy or by halogen; and R_2 represents hydrogen, or a pharmaceutically acceptable salt thereof.

7. A compound of the formula I according to claim 4, in which R_1 represents a thiazolyl radical, a 1-C_1-C_4-alkyl-imidazol-2-yl or -4-yl radical or a phenyl-C_1-C_4-alkyl-imidazol-2-yl or -4-yl radical each of which is unsubstituted or is C-substituted by C_1-C_4-alkyl, by C_1-C_4-alkoxy, by phenyl, by hydroxy, by

di-C_1-C_4-alkylamino, by C_1-C_4-alkylthio or by halogen having an atomic number of up to and including 35, and R_2 represents hydrogen, or a pharmaceutically acceptable salt thereof.

8. A compound of the formula I according to claim 4, in which R_1 represents a thiazol-2-yl radical that is unsubstituted or is mono- or di-substituted by C_1-C_4-alkyl or by phenyl, or represents an imidazol-2-yl or benzimidazol-2-yl radical that is unsubstituted or is mono-substituted in the 1-position by C_1-C_4-alkyl or by phenyl-C_1-C_4-alkyl, respectively, or represents an unsubstituted benzoxazol-2-yl or benzothiazol-2-yl radical, and R_2 represents hydrogen, or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 4 being 1-(thiazol-2-ylamino)methane-1,1-diphosphonic acid or a salt thereof.

10. A compound according to claim 4 selected from
1-(5-methyl-1,3,4-thiadiazol-2-ylamino)methane-1,1-diphosphonic acid or a salt thereof,
1-(1,3,4-thiadiazol-2-ylamino)methane-1,1-diphosphonic acid or a salt thereof,
1-(1-methylimidazol-2-ylamino)methane-1,1-diphosphonic acid or a salt thereof,
1-(oxazol-2-ylamino)methane-1,1-diphosphonic acid or a salt thereof,
1-(3-phenyl-1,2,4-thiadiazol-5-ylamino)methane-1,1-diphosphonic acid or a salt thereof,

1-(benzimidazol-2-ylamino)methane-1,1-diphosphonic acid or a salt thereof,

1-(benzothiazol-2-ylamino)methane-1,1-diphosphonic acid or a salt thereof,

1-(benzoxazol-2-ylamino)methane-1,1-diphosphonic acid or a salt thereof,

1-(4-methylthiazol-2-ylamino)methane-1,1-diphosphonic acid or a salt thereof,

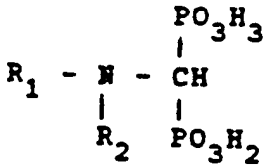
1-(5-methylthiazol-2-ylamino)methane-1,1-diphosphonic acid or a salt thereof,

1(5-phenylthiazol-2-ylamino)methane-1,1-diphosphonic acid or a salt thereof, and

1-(4-phenylthiazol-2-ylamino)methane-1,1-diphosphonic acid or a salt thereof.

11. A pharmaceutical composition containing a compound of formula I according to any one of claims 4 to 10 or a pharmaceutically acceptable salt thereof, in admixture with a conventional carrier or auxiliary.

12. A pharmaceutical composition containing a heteroarylmethanediphosphoric acid of the formula



(I)

in which R_1 represents a pyrazol-3-yl or isoxazol-3-yl radical that is optionally substituted by C_1-C_7 alkyl or by halogen, and

R_2 denotes hydrogen, or a pharmaceutically acceptable salt thereof in admixture with a conventional carrier or auxiliary.

13. Use of a compound according to any one of claims 4 to 10 to treat an illness associated with a calcium metabolism disorder in a warm-blooded animal.

14. A commercial package comprising a pharmaceutically effective amount of a compound according to any one of claims 4 to 10 together with instructions for use thereof to treat an illness associated with a calcium metabolism disorder in a warm-blooded animal.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS

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